PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
34104-0074		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA98/01137	08/12/1998	04/02/1998

International Patent Classification (IPC) or national classification and IPC
C12N15/10

Applicant
THE ONTARIO CANCER INSTITUTE et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/08/1999	02.06.00

Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich	Ury, A

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/01137

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-34	as originally filed				

Claims, No.:

6 (part),7-26	as originally filed				
1-5,6 (part)	as received on	13/05/2000	with letter of	04/05/2000	

Drawings, sheets:

1/6-6/6	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventiv step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4, 6, 14, 15, 18-25
	No:	Claims	1-3, 5, 7-13, 16, 17, 26
Inventive step (IS)	Yes:	Claims	18-25
	No:	Claims	1-17, 26
Industrial applicability (IA)	Yes:	Claims	1-16, 18-23, 26
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Item I.

The amendments filed with the letter dated 04.05.00 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:
- Claim 1, lines 1-3.
No basis for these amendments can be found in the application as filed.

Consequently, this report has been established as if said amendments had not been made (Rule 70.2(c) PCT), i.e. **has been established on the basis of claims 1-26 as originally filed.**

Item V.

Reference is made to the following documents:

D1: J. Bacteriol., 172(2), 1990, pp.653-8.
D2: J. Bacteriol., 173(3), 1991, pp.1151-60.
D3: Biotechniques, 17(6), 1994, pp.1132-39.
D_A: Bray et al., Abstract no. 428.
D_B: Bray et al., Abstract no. 429.

I) 1) Document D1 discloses a method for identifying cytotoxic mutant proteins capable of binding to a target cell, comprising steps (A), (B) and (C) of claim 1.
The specific embodiments recited in dependent claims 2, 3, 5, 7-13 and 16 are also disclosed in D1.
The method of claim 17 is also described in D1.
Thus, D1 destroys the novelty of present claims 1-3, 5, 7-13 and 16-17 (Article 33.2 PCT).

2) D2 as well destroys the novelty of claims 1-3, 5, 7-13 and 16-17 (Article 33.2 PCT).

II) The features of claims 4, 14, 15 and claim 6 (see e.g. document D3) are merely straightforward possibilities from which the skilled person would select, in accord-

ance with circumstances, without the exercise of inventive skill.
Therefore, the subject-matter of claims 4, 14, 15 and 6 lack an inventive step (Article 33.3 PCT) in view of D1 or D2 combined with the skilled person's general knowledge and D3, respectively.

III) Since said "suitable supports" are not defined in claim 26, the kit comprising said heteromeric protein toxin is anticipated by any disclosure of a heteromeric protein toxin. Claim 26 lacks novelty over *inter alia* D1 or D2.

IV) For the assessment of the present claims 17, 24 and 25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V) This Report is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the documents D_A and D_B cited in the international search report could become relevant.

Item VIII.

Claim 21 is not clear. It is directed to a method for constructing diagnostic probes for detecting the presence of a cell surface marker. Only step (A) is compulsory, steps (B) and (C) being optional. However, step (A) is not sufficient to perform the detection. At least step (C) should be performed. Thus, the word "optionally" renders the claim unclear (Article 6 PCT).

WE CLAIM:

1. A method for identifying cytotoxic mutant proteins of a cytotoxic wild type protein, said cytotoxic mutant protein capable of binding to a target cell which the wild type protein does not selectively bind to, comprising:

(A) selecting a heteromeric protein toxin having a toxic subunit and a binding subunit;

(B) generating a library of microorganism clones producing variant protein toxins of said heteromeric protein toxin by incorporating mutations into the binding subunit DNA of the heteromeric protein toxin; and

(C) screening the variant protein toxins of said library against said target cell by isolating clones or pools of clones producing said variant protein toxins, treating preparations of said target cell with said variant protein toxins, and selecting a cytotoxic mutant protein or pool of cytotoxic mutant proteins that inhibits or kills said target cell.

2. The method as claimed in claim 1, wherein said target cell is eukaryotic.

3. The method as claimed in claim 1, wherein said library comprises bacteria or bacterial supernatants containing said variant protein toxins.

4. The method as claimed in claim 1, wherein said library comprises yeast or yeast supernatants containing said variant protein toxins.

5. The method as claimed in claim 1, wherein said binding subunit DNA is in a plasmid in said microorganism.

6. The method as claimed in claim 1, wherein said mutation is incorporated into said binding subunit by use of a combinatorial cassette method comprising:

(A) preparing synthetic mutant oligonucleotides capable of annealing with a corresponding wild type oligonucleotide from said binding subunit;

(B) annealing said synthetic oligonucleotide from said binding subunit to an